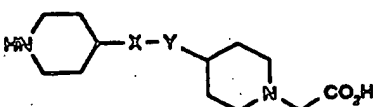
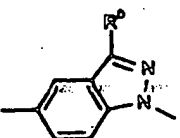
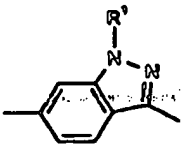




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification 6 : C07D 401/14, A61K 31/415, 31/445</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/49699 (43) International Publication Date: 31 December 1997 (31.12.97)</p>
<p>(21) International Application Number: PCT/EP97/03196 (22) International Filing Date: 19 June 1997 (19.06.97) (30) Priority Data: 9613017.4 21 June 1996 (21.06.96) GB 9613018.2 21 June 1996 (21.06.96) GB 9613095.0 21 June 1996 (21.06.96) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ALLEN, David, George [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). ELDRED, Colin, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JUDKINS, Brian, David [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). MITCHELL, William, Leonard [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).</p>		<p>(74) Agent: LEAROYD, Stephanie, Anne; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: PIPERIDINE ACETIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT OF THROMBOTIC DISORDERS</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(a)</p> </div> <div style="text-align: center;">  <p>(b)</p> </div> </div> <p>(57) Abstract</p> <p>The invention relates to compounds of formula (I) or a salt, solvate, or physiologically functional derivative thereof, in which X represents either CH₂-CH₂ or CH=CH; Y represents a group (a) or (b); R⁰ represents SO₂Me or CONH₂, and R¹ represents SO₂Me, to processes for their preparation, to pharmaceutical compositions containing such compounds and to their use in medicine, particularly in the treatment of thrombotic disorders.</p>		

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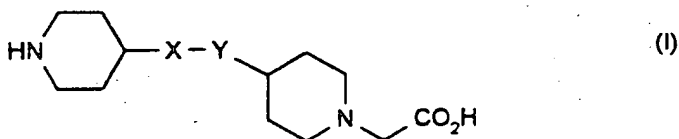
PIPERIDINE ACETIC ACID DERIVATIVES AND THEIR USE IN THE TREATMENT OF THROMBOTIC DISORDERS

This invention relates to acetic acid derivatives, to processes for their preparation, to pharmaceutical compositions containing such compounds and to their use in medicine.

It is widely accepted that the glycoprotein complex Gp IIb/IIIa is the fibrinogen binding site on platelets that mediates the adhesive function required for platelet aggregation and thrombus formation. We have now found a group of non-peptidic compounds which inhibit fibrinogen-dependent platelet aggregation by blocking the binding of fibrinogen to the putative fibrinogen receptor Gp IIb/IIIa complex.

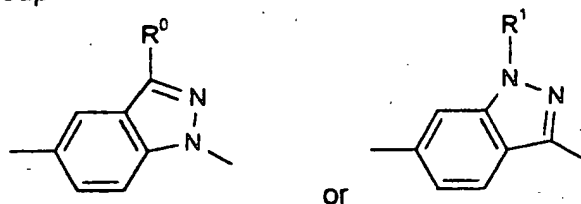
Co-pending applications WO96/20192 and WO96/41803, which were published after the priority date of the current invention, describe compounds which act as inhibitors of fibrinogen-dependent platelet aggregation, processes for their preparation and their use in medicine.

The current invention thus provides a compound of formula (I)



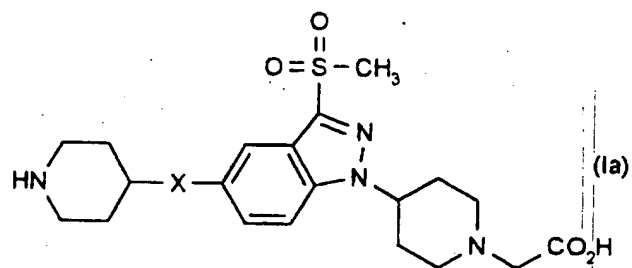
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or a salt, solvate, or physiologically functional derivative thereof, in which:
X represents either CH₂-CH₂ or CH=CH;
Y represents a group



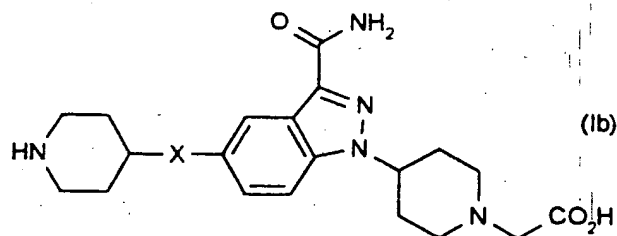
25 R⁰ represents SO₂Me or CONH₂; and
R¹ represents SO₂Me.

In a further aspect, the present invention provides a compound of formula (Ia)



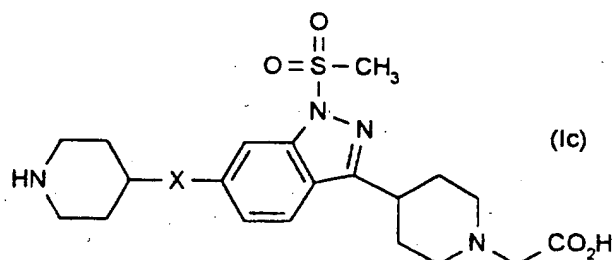
or a salt, solvate, or physiologically functional derivative thereof, in which:
X represents either $\text{CH}_2\text{-CH}_2$ or CH=CH .

- 5 In a yet further aspect, the present invention provides a compound of formula (Ib)



- 10 or a salt, solvate, or physiologically functional derivative thereof, in which:
X represents either $\text{CH}_2\text{-CH}_2$ or CH=CH .

In yet another further aspect, the present invention provides a compound of formula (Ic)



- 15 or a salt, solvate, or physiologically functional derivative thereof, in which:
X represents either $\text{CH}_2\text{-CH}_2$ or CH=CH .

Suitable compounds of the invention include:

- 20 {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}
acetic acid;

{4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ;
and salts, solvates, and physiologically functional derivatives thereof.

5 Further suitable compounds of the invention include:
{4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
{4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
10 and salts, solvates, and physiologically functional derivatives thereof.

Yet further suitable compounds of the invention include:
{4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
15 {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
and salts, solvates, and physiologically functional derivatives thereof.

A preferred compound of the invention is {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid or a salt, solvate, or
20 physiologically functional derivative thereof.

A further preferred compound of the invention is {4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid or a salt, solvate, or
25 physiologically functional derivative thereof.

A yet further preferred compound of the invention is {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid, or a salt, solvate, or physiologically functional derivative thereof.

30 All references herein below to "compounds of formula (I)" or "compounds of the present invention" or the like, refer to compound(s) of formula (I) and formulae (Ia)-(Ic) as described above, and their salts, solvates, or physiologically functional derivatives thereof.

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By the term "physiologically functional derivatives" is meant chemical derivatives of compounds of formula (I) which have the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. According to the present invention, examples of
5 physiologically functional derivatives include compounds of formula (I) in which the carboxyl function has been modified, for example, as a carboxylic acid ester, such as a C₁₋₆alkyl ester.

Salts and solvates of compounds of formula (I) which are suitable for use in
10 medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having a non-pharmaceutically acceptable counterion or associated solvent are within the scope of the present invention having use as intermediates in the preparation of compounds of formula (I) and their pharmaceutically acceptable salts, solvates,
15 and physiologically acceptable derivatives.

Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates,
20 naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphonates, ascorbates, tartrates, salicylates, succinates, lactates, glutarates, glutaconates, acetates, tricarballicates, citrates, fumarates and maleates) and inorganic base salts such as alkali metal salts (for example sodium salts). Hydrochloride salts of the compounds of formula (I) are preferred for certain
25 modes of administration. Other salts of the compounds of formula (I) include salts formed with trifluoro-acetic acid.

Suitable pharmaceutically acceptable solvates of the compounds of formula (I) include hydrates.
30

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their salts, solvates, and physiologically functional derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

5

By the term "pharmaceutically acceptable derivative" is meant a pharmaceutically acceptable salt, solvate, or physiologically functional derivative of a compound of formula (I) as hereinbefore defined.

- 10 Compounds of formula (I) inhibit blood platelet aggregation as demonstrated by studies performed on human washed and resuspended platelets (HRP) using a Born-type optical aggregometer (Born, G.V., 1962, Nature, 194, 927-929).

- 15 In view of their fibrinogen antagonist activity, the compounds of formula (I) and their pharmaceutically acceptable derivatives are of interest for use in human and veterinary medicine, particularly in the treatment of thrombotic disorders. Particular examples of thrombotic disorders are known in the art and include occlusive vascular diseases such as myocardial infarction, cardiac fatalities, angina, transient ischaemic attacks and thrombotic stroke, arteriosclerosis, vessel wall disease, peripheral vascular disease, nephropathy, retinopathy, postoperative thrombosis, pulmonary embolism, deep vein thrombosis and retinal vein thrombosis. The compounds of formula (I) and their pharmaceutically acceptable derivatives are also of interest for use in the prophylactic treatment of peri- and postoperative complications following organ transplantation (particularly cardiac and renal), coronary artery bypass, peripheral artery bypass, angioplasty, thrombolysis and endarterectomy.

- 25 The compounds of formula (I) and their pharmaceutically acceptable derivatives may also be useful for the treatment of other conditions in which the glycoprotein complex Gp IIb/IIIa or other integrin receptors are implicated. Thus, for example, the compounds of formula (I) and their pharmaceutically acceptable derivatives may potentiate wound healing and be useful in the treatment of bone conditions caused or mediated by increased bone resorption. Particular examples of bone diseases are known in the art and include osteoporosis, hypercalcaemia of malignancy, osteopenia due to bone
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- 35

metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia and glucocorticoid treatment.

- 5 The compounds of formula (I) and their pharmaceutically acceptable derivatives may also be useful for the treatment of certain cancerous diseases, for example, to prevent or delay metastasis in cancer.

10 According to a further aspect of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine, particularly for use in the treatment of thrombotic disorders.

15 According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor.

20 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

25 According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of thrombotic disorders.

30 According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a thrombotic disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

It is to be understood that reference to "treatment" includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

5 It will be appreciated that the compounds of formula (I) and their pharmaceutically acceptable derivatives may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include thrombolytic agents or any other compound stimulating thrombolysis or fibrinolysis and cytotoxic drugs. It is to
10 be understood that the present invention covers the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in combination with one or more other therapeutic agents.

The compounds of formula (I) and their pharmaceutically acceptable derivatives
15 are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine. Such compositions may conveniently be presented for use in conventional
20 manner in admixture with one or more physiologically acceptable carriers or excipients.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner. The compounds
25 may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions
30 prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch. In a preferred aspect, the present invention provides an iontophoretic delivery
35 device (for example, an iontophoretic patch) comprising a compound of formula

(I) or a pharmaceutically acceptable derivative thereof, suitably a pharmaceutically acceptable salt thereof, for example, a hydrochloride salt. Iontophoretic devices and systems as such are known in the art, for instance from, WO-A 9116946, WO-A 9116944, WO-A 9116943, WO-A 9115261, WO-A 9115260, WO-A 9115259, WO-A 9115258, WO-A 9115257, WO-A 9115250, WO-A 9109645, WO-A 9108795, WO-A 9004433, WO-A 9004432, WO-A 9003825, EP-A 254965, US 4717378, EP-A 252732 and GB-A 2239803, which are incorporated herein by reference.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of formula (I) and their pharmaceutically acceptable derivatives may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent, in particular a thrombolytic agent.

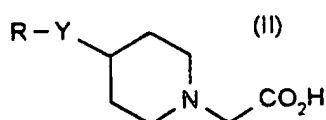
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

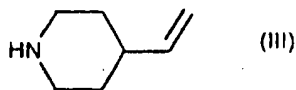
A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01 mg/kg to 30 mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.1mg/kg to 10mg/kg may be suitable for systemic administration.

Compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure, for example, by the methods described below.

Thus, according to a first process (A), compounds of formula (I) may be prepared by reacting a compound of formula (II)



or a protected derivative thereof, wherein Y is defined as for formula (I) and R represents a leaving group, for example, chloro, bromo or iodo, or a -OSO₂CF₃ group, with the compound of formula (III)



or a protected derivative thereof, in the presence of a transition metal catalyst and at elevated temperature. Suitable transition metal catalysts include palladium catalysts, such as a palladium triarylphosphine catalyst. Suitable temperatures are from about 20 to about 160°C, such as 80 to 120°C, or the reflux temperature of the solvent. Conveniently the reaction is effected in the presence of a base, such as a tertiary amine, and in a solvent, such as a polar solvent, for example *N,N*-dimethylformamide.

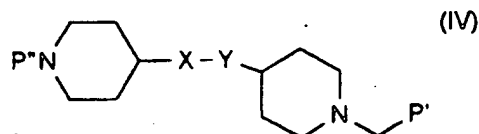
According to another process (B) compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors.

For example, compounds of formula (I) in which X represents CH₂-CH₂ may be prepared from the corresponding compounds of formula (I), or protected derivatives thereof, in which X represents CH=CH by hydrogenation. The hydrogenation may be effected in the presence of a transition metal catalyst, such as Raney Nickel, or a palladium, platinum or rhodium catalyst. Conveniently the reaction is effected in a solvent, such as an alcohol (e.g. ethanol).

Alternatively, hydrogenation may be effected chemically, for example, by using diimide. Conveniently the diimide is generated *in situ* from a suitable salt, such as diazenedicarboxylic acid, dipotassium salt, and the reaction is effected in the presence of an acid, such as acetic acid, and a solvent, such as an alcohol (e.g. methanol).

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the above described processes to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

Another process (C) for preparing compounds of formula (I) thus comprises deprotecting a compound of formula (IV)



wherein X and Y are as defined for a compound of formula (I), P' is a carboxyl group or a protected carboxyl group and P'' is hydrogen or an amino protecting group, provided that when P' is a carboxyl group, P'' is not hydrogen and when P' is a hydrogen, P'' is not a carboxyl group.

Compounds of formula (IV) may be prepared by processes (A) and (B) as described above, or using any appropriate methods, such as those described in the examples.

10

In a particular embodiment of process (C), compounds of formula (I) may be prepared from protected carboxyl derivatives of compounds of formula (I), ie. compounds of formula (IV) wherein P' is a protected carboxyl group. In a further embodiment of this process, compounds of formula (I) may be prepared from protected amino and/or carboxyl derivatives of compounds of formula (I), ie. compounds of formula (IV) wherein P'' is an amino protecting group.

15

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W. Green, second edition, (John Wiley and Sons, 1991), which also describes methods for the removal of such groups.

20

Particular protected carboxyl groups include, for example, carboxylic acid ester groups such as carboxylic acid alkyl or aralkyl esters, for example where the alkyl or aralkyl portion of the ester function is methyl, ethyl, tert-butyl, methoxymethyl, benzyl, diphenylmethyl, triphenylmethyl or p-nitrobenzyl. When the ester is an unbranched alkyl (e.g. methyl) ester deprotection may be effected under conditions of either basic hydrolysis, for example using lithium hydroxide, or acidic hydrolysis, for example using hydrochloric acid. Tert-butyl and triphenylmethyl ester groups may be removed under conditions of acid hydrolysis, for example using formic or trifluoroacetic acid at room temperature or using hydrochloric acid in acetic acid. Benzyl, diphenylmethyl and

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nitrobenzyl ester groups may be removed by hydrogenolysis in the presence of a metal catalyst (e.g. palladium).

5 Particular amino protecting groups include, for example, aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzylloxycarbonyl, t-butoxycarbonyl or trifluoroacetyl groups. Removal of acyl groups may be effected under standard conditions as referred to above.

10 When a particular isomeric form of a compound of formula (I) is desired the required isomer may conveniently be separated using preparative high performance liquid chromatography (h.p.l.c.) applied to the final title compounds of processes (A) to (C) above or applied prior to any final deprotection step in said processes.

15 Compounds of formula (II) and (IV), or protected derivatives thereof, may be prepared using any appropriate methods, such as those described in the examples.

20 Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention. Compounds of formula (II), for example, [4-(5-bromo-3-methanesulfonyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester, and 5-bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester, are key intermediates and represent a particular aspect of the present invention. The compounds of formula (IV) are also an important aspect of the present invention and include 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-methane-sulfonyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester, 1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester, 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-carbamoyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester, and 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1-methanesulfonyl-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester.

25

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Conveniently, compounds of the invention are isolated following work-up as acid addition salts, e.g. trifluoroacetate or hydrochloride salts. Pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared from the corresponding trifluoroacetate salts by exchange of ion using conventional means, for example by neutralisation of the trifluoroacetate salt using a base such as aqueous sodium hydroxide, followed by addition of a suitable organic or inorganic acid, for example, hydrochloric acid. Alternatively, pharmaceutically acceptable acid addition salts may be prepared directly by effecting deprotection with the appropriate organic or inorganic acid, for example, hydrochloric acid. Inorganic base salts of the compounds of the invention may also be prepared from the corresponding trifluoroacetate salts by addition of a suitable strong base such as sodium hydroxide.

Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

The following Examples illustrate the invention but do not limit the invention in any way. All temperatures are in °C. Thin layer chromatography (T.l.c.) was carried out on silica plates. Preparative high performance liquid chromatography (h.p.l.c.) was carried out, unless otherwise indicated, using a Dynamax 60Å C18 8µM 25cm x 41.4mm i.d. column eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water and (ii) acetonitrile, the eluant being expressed as the percentage of (ii) present in the solvent mixture, at a flow rate of 45ml per minute. Analytical h.p.l.c. was carried out, unless otherwise indicated, using a Dynamax 60Å C18 8µM 25 cm x 4.6mm i.d. column eluted with a mixture of solvents consisting of (i) and (iii), 0.05% trifluoroacetic acid in acetonitrile, the eluant being expressed as the percentage of (iii) present in the solvent mixture, at a flow rate of 1ml per minute. The following abbreviations are used: Me = methyl; Et = ethyl; THF = tetrahydrofuran; DMF = N,N-dimethylformamide; and RT = hplc retention time.

Example 1

Synthesis of {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate)

(i) 5-Bromo-2-nitro-2H-indazole

To stirred acetic anhydride (410ml) at -5° was added, dropwise, fuming nitric acid (8.5ml). After 20 min. the solution was cooled to -15° and 5-bromoindazole¹ (7.70g) was added portionwise maintaining the temperature at -15°. The mixture was stirred at -15° for 2h, added to iced water (1l), and vigorously stirred for a further 2h. The solid was collected by filtration and was partitioned between diethyl ether and 5M aqueous sodium hydroxide. The aqueous layer was extracted with diethyl ether and the combined organic extracts were dried (Na₂SO₄) and evaporated *in vacuo* to afford the title compound as an orange solid (7.45g).

Mass spectrum m/z 243 (MH⁺)

¹Ref: C. Dell'Erba et al, Tetrahedron, 1994, 50, 3529.

(ii) 5-Bromo-3-methanesulfonyl-1H-indazole

A mixture of 5-bromo-2-nitro-2H-indazole (3.12g) and sodium methanesulfinate (2.89g) in DMF (20ml) was stirred at 20° for 5h. The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a yellow solid (1.88g).

Mass spectrum m/z 294 (MNH₄⁺)

(iii) 4-(5-Bromo-3-methanesulfonyl-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

A stirred mixture of 5-bromo-3-methanesulfonyl-1H-indazole (1.20g), 4-methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester² (1.58g), potassium carbonate (1.81g) and N,N-dimethylformamide (20ml) was heated at 100° for 18h. The cooled mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate:cyclohexane 1:5 to give the title compound as a cream solid (1.37g).

Mass spectrum m/z 459 (MH⁺)

²Ref: EP-A-0 560 268 A1

(iv) 5-Bromo-3-methanesulfonyl-1-piperidin-4-yl-1H-indazole

A solution of 4-(5-bromo-3-methanesulfonyl-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.36g) in trifluoroacetic acid (10ml) was stirred at 20° for

1.5h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane and 0.5M aqueous sodium hydroxide. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a cream solid (0.90g).

Mass spectrum m/z 360 (MH^+)

(v) 4-(5-Bromo-3-methanesulfonyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

A mixture of 5-bromo-3-methanesulfonyl-1-piperidin-4-yl-1H-indazole (0.90g), tert-butylbromoacetate (0.390ml) and sodium bicarbonate (0.380g) in N,N-dimethylformamide (15.0ml) was stirred at 20° for 20h. The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane, and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel (Merck 9385), eluting with ethyl acetate-cyclohexane (gradient 1:4 to 1:3) to give the title compound as a cream solid (0.870g).

Mass spectrum m/z 474 (MH^+)

(vi) 4-[2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-methanesulfonyl-1H-indazol-5-yl]-(E)-vinyl]-piperidine-1-carboxylic acid tert-butyl ester

A stirred mixture of [4-(5-bromo-3-methanesulfonyl-indazol-1-yl)-piperidin-1-yl]-acetic acid tert-butyl ester (0.350g), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester³ (0.177g), triethylamine (0.320ml), palladium (II) acetate (0.014g), tri-*o*-tolylphosphine (0.037g) and N,N-dimethylformamide (2.50ml), was heated at 110° under nitrogen for 16h. The cooled mixture was concentrated *in vacuo* and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel (Merck 9385), eluting with dichloromethane : ethanol : 880 ammonia (80:18:2) to give the title compound as a white solid (0.270g).

Mass spectrum m/z 603 (MH^+)

³Ref: PCT/EP95/05043

(vii) {4-[3-Methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate salt

5 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-methanesulfonyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (0.270g) was dissolved in trifluoroacetic acid (10ml) and the mixture was stirred at 20° for 5 h. The mixture was concentrated *in vacuo*, and the residue purified by trituration with diethyl ether. The resulting solid was collected by filtration and dried *in vacuo* to afford the title compound as a cream solid (0.170g).

10 Mass spectrum m/z 447 (MH⁺)

Analysis: Found: C, 42.0; H, 3.9; N, 6.8; S, 3.9

C₂₂H₃₀N₄O₄S.3.2CF₃CO₂H requires: C, 42.0; H, 4.1; N, 6.9; S, 3.95%

Example 2

15 Synthesis of {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate salt.

Method A

{4-[3-Methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid tris(trifluoroacetate) (0.782g) was hydrogenated at room temperature and pressure over 10% palladium on carbon (50% paste, 0.20g) in water:ethanol 70:30 for 6h. The catalyst was filtered off and the solvent evaporated *in vacuo* to give a yellow oil (0.577g). Purification by preparative HPLC (gradient profile 10-75% (ii) in 20min, detection 250nm, RT 10.3min) and trituration of the resulting gum with dry ether gave the title compound as a white solid (0.180g).

25 Mass spectrum m/z 449 (MH⁺)

Analysis Found: C, 44.6; H, 5.2; N 7.8; S, 4.3.

C₂₂H₃₂N₄O₄S.2.4CF₃COOH requires: C, 44.6; H 4.8; N 7.8; S, 4.4.

30 Method B

(a) 4-Bromo-(2-methylthiomethyl)aniline

Dimethylsulfide (105 ml) was added dropwise to a stirred solution of N-chlorosuccinimide (139.7 g) in dichloromethane (3750 ml) at 0 to -5 °C and the resulting suspension cooled to -20°C. To this was added dropwise a solution of 4-bromoaniline (150.0 g) in dichloromethane (300 ml), the suspension stirred at

-20°C for 0.5h and the reaction mixture diluted with triethylamine (292 ml). The reaction mixture was stirred at ambient temperature for 58h, washed with water, 2N hydrochloric acid, 8% w/w aqueous sodium bicarbonate, dried (MgSO₄) and evaporated in vacuo to give the title compound as a pale yellow solid (162.0 g).
5 Mass spectrum m/z 232.9 (MH⁺)

(b) 5-Bromo-3-methylsulfanyl-1H-indazole

A solution of sodium nitrite (48.4 g) in water (100 ml) was added dropwise to a stirred solution of 4-bromo-(2-methylthiomethyl)aniline (163.0 g) and fluoboric acid (230 ml, 48%w/w aqueous solution) in water (815 ml) at 10-15 °C. The
10 resulting yellow suspension was stirred at ambient temperature for 1h, the solid isolated by filtration, the solid washed with water and diethylether and finally suspended in chloroform (4000 ml). The stirred suspension was treated with potassium acetate (138.0 g) and 18-Crown-6 (9.30 g) and stirred at ambient
15 temperature for 2h. The reaction mixture was filtered and the filtrate washed with 2N sodium hydroxide, dried (MgSO₄) and evaporated in vacuo to give the title compound as a pale yellow solid (147.7 g).
Mass spectrum m/z 243.9 (MH⁺)

20 (c) 5-Bromo-3-methanesulfonyl-1H-indazole

Oxone™ (182.2 g) was added portionwise to a stirred suspension of 5-bromo-3-methylsulfanyl-1H-indazole (36.0 g) in methanol (450 ml) and water (135 ml). The reaction mixture was stirred at ambient temperature for 3h, concentrated in vacuo and the resulting oil partitioned between ethyl acetate and water. The
25 biphasic mixture was separated, the aqueous phase extracted with ethyl acetate, the combined organic extracts were washed with 8 %w/w aqueous sodium bicarbonate and water, dried (MgSO₄) and evaporated in vacuo to give the title compound as a off-white solid (38.8 g).
Mass spectrum m/z 293.9 (MNH₄⁺)

30

(d) 4-[3-Methanesulfonyl-5-{1-(1-tert-butoxycarbonylmethyl-2-piperidin-4-yl-ethyl)}-1H-indazol-1-yl]-1-piperidine acetic acid tert-butylester

A solution of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-methanesulfonyl-1H-indazol-5-yl]-(E)-vinyl}-1-piperidine acetic acid tert-butyl
35 ester (77.0 g) in ethanol (760 ml) was added to a pre-hydrogenated suspension

of 10% Pd/C (115.5g) in ethanol (77 ml) and water (19 ml) and the resulting stirred suspension hydrogenated at ambient temperature for 26h. The reaction was filtered through hyflo, the residue washed with ethanol and the combined filtrate evaporated in vacuo to give a pale green oil which was purified by

5 Biotage chromatography, eluting with ethyl acetate : cyclohexane (1:1), to give the title compound as a gum-solid (46.8 g).

Mass spectrum m/z 605.3 (MH⁺)

10 (e) 4-[3-Methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-1H-indazol-1-yl]-1-piperidine acetic acid dihydrochloride

A solution of 4-[3-Methanesulfonyl-5-{1-(1-tert-butoxycarbonylmethyl-2-piperidin-4-yl-ethyl)}-1H-indazol-1-yl]-1-piperidine acetic acid tert-butylester (25.0 g) in trifluoroacetic acid (250 ml) was stirred at ambient temperature for 4h. The reaction mixture was evaporated in vacuo and the residue purified by

15 preparative HPLC, eluting with water : acetonitrile : trifluoroacetic acid (gradient 90:10:0.1 to 25:75:0, 20 min, detection 260nm, RT 13 min), to give a white solid which was dissolved in 2N hydrochloric acid and evaporated in vacuo to give the a white solid. The hydrochloric acid procedure was repeated twice. The

20 white solid was triturated with acetone (100 ml) and the suspension evaporated in vacuo. The solid was again triturated with acetone (100 ml), the suspension stirred at ambient temperature for 0.5h and the solid isolated by filtration, washed with acetone and dried in vacuo at 45°C to constant weight to give the title compound as a white crystalline solid (10.03 g).

25 Analysis found:

C, 46.9; H, 6.8; N, 9.9

C₂₂H₃₂N₄O₄ S.2HCl.2H₂O requires: C, 47.3; H, 6.8; N, 10.0 %

Example 3

30 Synthesis of {4-[3-Carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

(a) 5-Bromo-1-(1-tert-butoxycarbonyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester

5-Bromo-1H-indazole-3-carboxylic acid⁴, methyl ester (35.8g) in dry THF (400ml) containing 4-methanesulphonyloxy-piperidine-1-carboxylic acid tert-

35 butyl ester² (40.9g, 153mmol) was treated with potassium t-butoxide (15.75g,

140mmol) and stirred at reflux under nitrogen for 24h. When cool, the mixture was evaporated *in vacuo* and the residue treated with aqueous saturated ammonium chloride (400ml). The mixture was extracted with ethyl acetate and the combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* onto silica gel. The resultant silica was applied as a plug to a flash column of silica gel, eluting with cyclohexane:ethyl acetate (gradient 19:1 to 3:1) to give firstly an isomer followed by the title product (22.8g).

T.l.c. SiO_2 (cyclohexane:EtOAc, 7:3), Rf 0.29.

Ref⁴ G.A. Bistocchi *et al.*, Farmaco. Ed. Sci., 1981, 36, 315.

(b) 5-Bromo-1-piperidin-4-yl-1H-indazole-3-carboxylic acid methyl ester bis(trifluoroacetate)

Trifluoroacetic acid (100ml) was added to 5-bromo-1-(1-tert-butoxycarbonyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester (22.75g) at 23° during 1 min. After 1h, the mixture was evaporated *in vacuo* and the co-evaporated with dichloromethane to give the title product (28.05g) as a light yellow solid.

T.l.c. SiO_2 (CH_2Cl_2 :EtOH:880 NH_3 , 89:10:1), Rf 0.18.

(c) 5-Bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester

A solution of 5-bromo-1-piperidin-4-yl-1H-indazole-3-carboxylic acid methyl ester bis(trifluoroacetate) (28.05g) and tert-butylbromoacetate (7.3ml) in DMF (500ml) was treated with diisopropylethylamine (25.9ml) under nitrogen with stirring at 23° and kept for 4 days. Further tert-butylbromoacetate (1.4ml), followed by diisopropylethylamine (5.0ml) were added and stirring continued for 2h. The mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (400ml), and extracted with ethyl acetate. The combined, dried (Na_2SO_4) organic extracts were evaporated *in vacuo* and the residue crystallised from ethyl acetate to give the title product (13.43g).

T.l.c. SiO_2 (Cyclohexane:EtOAc, 7:3) Rf 0.17.

(d) 1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester

A mixture of 5-bromo-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-3-carboxylic acid methyl ester (13.43g), 4-vinyl-piperidine-1-carboxylic

acid tert-butyl ester(6.90g), palladium (II) acetate (666mg), tri-*o*-tolylphosphine (1.81g), triethylamine (12.4ml, 89.1mmol), and DMF (200ml) was stirred at 120° under nitrogen for 15h. When cool, the mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (200ml), and extracted with ethyl acetate. The combined, dried (Na₂SO₄) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with dichloromethane:ethanol:880 ammonia (gradient 989:10:1 to 978:20:2) to afford the title compound as a light orange foam (8.94g). T.l.c. SiO₂ (CH₂Cl₂:EtOH:880NH₃, 978:20:2) Rf 0.14.

(e) 4-{2-[1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-3-carbamoyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

1-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-5-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-(E)-vinyl]-1H-indazole-3-carboxylic acid methyl ester (600mg) in methanol (20ml) saturated with ammonia was heated at 80° for 50h. The cooled solution was evaporated *in vacuo* and the residue purified by flash chromatography over silica gel. Gradient elution with dichloromethane:ethanol:0.88 ammonia (gradient 989:10:1 to 967:30:3) afforded the title product as a white foam (373mg).

T.l.c. SiO₂ (CH₂Cl₂:EtOH:880NH₃, 978:20:2) Rf 0.08.

(f) {4-[3-Carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

A solution of 4-{2-[1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-3-carbamoyl-1H-indazol-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (292mg) in trifluoroacetic acid (6ml) was kept at 23° for 2h. The solution was evaporated *in vacuo*, co-evaporated with water (3ml), and triturated with diethyl ether to give the title product as a white solid (311mg).

Mass spectrum *m/z* 412 (MH⁺).

Analysis Found: C,45.0; H,4.8; N,9.4.

C₂₂H₂₉N₅O₃.2.8CF₃CO₂H requires C,45.4; H,4.4; N,9.6%.

Example 4

Synthesis of {4-[3-Carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

Method A

A solution of {4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid trifluoroacetate (100mg) in water (40ml) was added to a suspension of prehydrogenated 10% palladium on activated carbon (70mg) in water (10ml) and stirred under hydrogen for 4h. The catalyst was filtered off, washed, and the filtrate treated with trifluoroacetic acid (2 drops). The solution was evaporated *in vacuo*, and the residue was triturated with ether to give the title product as fine white crystals (74mg).

Mass spectrum. m/z 414.1 (MH⁺)

10 Analytical HPLC RT 9.2 min.

Analysis Found: C, 45.7 ; H, 4.9 ; N, 9.9.

C₂₂H₃₁N₅O₃·2.65 CF₃CO₂H requires C, 45.8; H, 4.7 ; N, 9.8 %.

Method B

15 (a) 5-bromo-3-formyl-1H-indazole

A solution of 5-bromoindole (100g) and sodium nitrite (350g) in 1,4-dioxane (3.5L) and water (18vol.) was acidified to pH 2.5 by the steady addition of 3N hydrochloric acid (18L) over 0.5h at 20-25°. The mixture was stirred for 0.75h and then extracted with ethyl acetate. The combined organic extracts were diluted with ethyl acetate (1L) and washed with water. The combined water washes were extracted with ethyl acetate. The organic layer was washed with water, combined with the main organic extract and evaporated to give a dark black-brown solid. This solid was triturated with ethyl acetate (200ml) for 1h, filtered and the filter cake washed with ethyl acetate and dried to give the title compound as a red-brown solid (60.8g).

25

Mass spectrum m/z 223, 225 [M-H⁺]

(b) 5-Bromo-3-cyano-1H-indazole

A suspension of 5-bromo-3-formyl-1H-indazole (143g) was heated to 65-70° in a solution of hydroxylamine-O-sulfonic acid (93.4) in water (1.4L) for 16h. The mixture was cooled to 20° over 1h, filtered and the filter cake washed with water and dried at 45°C to give a solid (146g). This solid was heated at reflux in toluene (3.65L) for 1h and filtered at 90°C. The filtrate was re-heated to give a solution, stirred and cooled to 10°. The suspension is filtered, the filter cake

30

washed with toluene and dried to give the title compound as a pale brown solid (111g).

Mass spectrum m/z 220, 222 [M-H⁺]

5 (c) 4-(5-Bromo-3-cyano-1H-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

A suspension of 5-bromo-3-cyano-1H-indazole (111g), 1-tert-butoxycarbonyl-4-methylsulphonyl-piperidine (168g) and potassium carbonate (193g) in DMF (1.1L) was heated at 105-110° for 6h, evaporated to dryness and the orange residue partitioned between dichloromethane and water. The aqueous phase was re-extracted with dichloromethane, the combined organics washed with water and evaporated to an orange residue (130g). This residue was triturated with a mixture of cyclohexane and ethyl acetate (6:1, 1.04L) for 1h and filtered. The filter cake was washed with a mixture of cyclohexane and ethyl acetate and dried to give the title compound as a pale yellow powder (125g).

Mass spectrum m/z 405, 407 [MH⁺]

(d) 5-Bromo-1-piperidin-4-yl-1H-indazole-3-carboxamide

4-(5-bromo-3-cyano-1H-indazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester (62g) was added portionwise over 1h at 20-30° to conc. sulfuric acid (620g) and the suspension stirred for 2h. The mixture was poured onto ice (1.24kg), basified to pH12 with 5N sodium hydroxide (2.44L) at 20-30° over 1.5h, diluted with water (300ml) and filtered. The filter cake was washed with water and dried to give the title compound as an off-white solid (51.5g).

Mass spectrum m/z 323, 325 [MH⁺]

(e) 4-(5-Bromo-3-aminocarbonyl-1H-indazol-1-yl)-1-piperidine acetic acid tert-butyl ester

tert-Butyl bromoacetate (60.4g) was cautiously added to a solution of 5-bromo-1-piperidin-4-yl-1H-indazole-3-carboxamide (100g) and triethylamine (43.3ml) in DMF (1L) at 20-30° and the mixture was stirred for 2h. Water (1.5L) was added dropwise over 1h to the mixture at <25°, the suspension stirred for 1h and filtered. The filter cake was washed with water and dried to give the title compound as a pale yellow solid (121g).

Mass spectrum m/z 437, 439 [MH⁺]

(f) 4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester.

- 5 A mixture of 4-(5-Bromo-3-aminocarbonyl-1H-indazol-1-yl)-1-piperidine acetic acid tert-butyl ester (120g), 4-(E)-vinyl-piperidine-1-carboxylic acid tert-butyl ester (60.8g), triethylamine (114.6ml), tri-ortho-tolylphosphine (16.7g), palladium acetate (6.2g) and harborlite J2 filter aid (60g) was heated at 105-110° in DMF (2.4L) for 14h. The mixture was cooled to ca.35°, charcoal (30g) was added and the mixture stirred for 1h at ca.35° before cooling to ambient temperature.
- 10 The mixture was filtered and the filter pad washed with N, N-dimethylformamide and cyclohexane. The combined filtrate was diluted with water (240ml), the phases separated and the N, N-dimethylformamide/water extract washed with cyclohexane and concentrated to a red gum. The gum was stirred in water (600ml) for 1h, further water (1.8L) was added and the suspension stirred for
- 15 0.5h and filtered. The filter cake was washed with water and dried to give the title compound (153g) as a yellow-orange solid.
- Mass spectrum m/z 568 [MH⁺]

(g) 4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester.

- 20 10% Palladium-carbon catalyst (73.5g) was added to a solution of 4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (147g) in tetrahydrofuran (2.94L) and stirred under a hydrogen atmosphere at ambient temperature for
- 25 5h. A second charge of 10% palladium-carbon catalyst (73.5g) and tetrahydrofuran (200ml) was added and the suspension stirred under hydrogen for a further 18h before a third charge of catalyst (73.5g) and tetrahydrofuran (200ml) was added and the suspension stirred under hydrogen for another 20h.
- 30 The mixture was filtered, washed with tetrahydrofuran and evaporated to a thick black oil. This oil was purified by Biotage chromatography over silica gel eluting with ethyl acetate-cyclohexane (1:1) and then ethyl acetate to give the title compound as white crystals (32.65g).
- Mass spectrum m/z 570 [MH⁺]

(h) {4-[3-Carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

4-{2-[3-Aminocarbonyl-1-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazole-5-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (32.65g) was added in two equal portions to trifluoroacetic acid (330ml) and the solution stirred at ambient temperature for 3h. The mixture was concentrated to 100g weight and purified by preparative HPLC (Kromsil C8, 10µm, reverse phase), eluting with water-acetonitrile-trifluoroacetic acid, 90:10:0.1%v/v (A) and water-acetonitrile, 25:75 (B) to give a white solid (26g). The solid (23.6g) was dissolved in HPLC grade water (60ml) and adjusted to pH10 with 880 ammonia solution (20ml) added at 20-30° over 0.5h. The milky-white suspension was stirred at 20° for 1.5h and filtered. The filter cake was washed with water with sucking under vacuum for 10min between each wash, dried at 40° for 18h and left to equilibrate under ambient conditions for 4h to give the title compound as a white powder (12.05g).

Mass spectrum m/z 414 [MH⁺]

Example 5

Synthesis of {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid.

(a) 1-[4-(2,4-Dibromo-benzoyl)-piperidin-1-yl]-ethanone

1,3-Dibromobenzene (65ml) was added to a stirred mixture of 1-acetyl-piperidine-4-carbonyl chloride hydrochloride⁵ (21.8g) and aluminium (III) chloride (34.5g) and the mixture heated at 95-100° for 1.5h. When cool, the mixture was poured into a mixture of ice-water (50ml) and extracted with ethyl acetate. The combined, dried (Na₂SO₄) organic extracts were evaporated *in vacuo* and the residue purified by flash chromatography over silica gel (Merck 9385). Gradient elution with ether - ethanol (gradient 99:1 to 90:10) afforded the title compound as an orange oil (16.7g).

T.l.c. SiO₂ (Et₂O - EtOH, 9:1) R_f = 0.23

Ref⁵ EP-A-0 428 437

(b) (2,4-Dibromo-phenyl)-piperidin-4-yl-methanone hydrochloride

A stirred mixture of 1-[4-(2,4-dibromo-benzoyl)-piperidin-1-yl]-ethanone (11.00g) and aqueous 5M hydrochloric acid (60ml) was heated under reflux under

nitrogen for 7h. The mixture was evaporated *in vacuo* to give the title compound as a white solid (10.8g).

T.l.c. SiO₂ (CH₂Cl₂-EtOH-880NH₃, 89:10:1) R_f = 0.17

5 (c) (2,4-Dibromo-phenyl)-piperidin-4-yl-methylene-hydrazine

A stirred solution of (2,4-dibromo-phenyl)-piperidin-4-yl-methanone hydrochloride (7.04g), hydrazine (6.0ml), and ethanol (150ml) was heated under reflux under nitrogen for 16h. The cooled solution was evaporated *in vacuo*, treated with aqueous 1M sodium carbonate (50ml), extracted with ether, and the combined, dried (Na₂SO₄) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography (Merck 9385) eluting with dichloromethane-ethanol-880 ammonia (gradient 89:10:1 to 835:150:15) to give the title compound as a cream solid (5.71g).

10 T.l.c. SiO₂ (CH₂Cl₂-EtOH-880 NH₃, 78:20:2) R_f = 0.13 (minor) and R_f = 0.16 (major)

15 (d) 6-Bromo-3-piperidin-4-yl-1H-indazole hydrochloride

A stirred mixture of (2,4-dibromo-phenyl)-piperidin-4-yl-methylene-hydrazine (5.64g), sodium hydride (1.25g, 60% dispersion in oil), and dry DMF (150ml) was heated at 105° under nitrogen for 6.5h. Further sodium hydride (200mg) was added and heating continued for 2h. The mixture was evaporated *in vacuo* acidified to pH 1 by the addition of aqueous 2M hydrochloric acid, and then basified to pH 8 by the addition of aqueous 1M sodium carbonate. The mixture was extracted with ether, and the combined, dried (Na₂SO₄) organic extracts were evaporated *in vacuo*. The residue was purified by flash chromatography (Merck 9385), eluting with dichloromethane - ethanol - 880 ammonia (gradient 89:10:1 to 78:20:2) to give the title compound as a cream-yellow solid (2.50g).

25 T.l.c. SiO₂ (CH₂Cl₂-EtOH-880NH₃, 78:20:2) R_f = 0.6

30 (e) [4-(6-Bromo-1H-indazol-3-yl)-piperidin-1-yl]-acetic acid tert-butyl ester

A mixture of 6-bromo-3-piperidin-4-yl-1H-indazole hydrochloride (500mg), tert-butyl bromoacetate (0.29ml), sodium bicarbonate (150mg, 1.87mmol), and DMF (10ml) was stirred at 23° under nitrogen for 18h. The mixture was evaporated *in vacuo*, treated with aqueous saturated sodium bicarbonate (25ml), and extracted with ethyl acetate (50ml). The dried (Na₂SO₄) organic layer was

evaporated *in vacuo* onto silica gel (Merck 7734). Purification by flash chromatography (Merck 9385), eluting with dichloromethane - ethanol - 880 ammonia (gradient 967:30:3 to 945:50:5) afforded the title compound as fine white crystals (347mg).

5 T.l.c. SiO₂ (CH₂Cl₂-EtOH-880 NH₃, 945:50:5) R_f = 0.27

(f) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

10 A mixture of [4-(6-bromo-1H-indazol-3-yl)-piperidin-1-yl]-acetic acid tert butyl ester (1.34g), 4-vinyl-piperidine-1-carboxylic acid tert-butyl ester (0.75g), triethylamine (1.4ml), palladium (ii) acetate (0.050g) and tri(o-tolyl)phosphine (0.210g) in DMF (60ml) was stirred at 120° under nitrogen for 16h. The mixture was evaporated *in vacuo* and purified by flash chromatography (Merck 9385), eluant ethyl acetate: cyclohexane: triethylamine (50:50:2 to 100:0:2), to give the

15 title compound as a yellow solid (1.18g).

T.l.c. SiO₂ (CH₂Cl₂ : EtOH: 880 NH₃ 95: 5: 0.5) R_f = 0.32

(g) 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1-methanesulfonyl-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester

20 A solution of 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (0.211g) in DMF (10ml) was treated with sodium hydride (60% dispersion in oil, 0.019g) and stirred for 0.5h at 23°C under nitrogen. Methanesulphonyl chloride (0.03ml) was added and the mixture stirred for a further 40h. The solvent was evaporated *in vacuo* and the residue was partitioned between water (20ml) and ethyl acetate. The

25 extracts were dried (Na₂SO₄), evaporated *in vacuo*, and purified by flash chromatography on silica gel, eluant cyclohexane: ether: triethylamine 50:50:2, to give the title compound as a colourless gum (0.141g).

Mass spectrum m/z 603 (MH⁺).

30

(h) {4-[1-Methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate

35 4-{2-[3-(1-tert-Butoxycarbonylmethyl-piperidin-4-yl)-1-methanesulfonyl-1H-indazol-6-yl]-(E)-vinyl}-piperidine-1-carboxylic acid tert-butyl ester (0.138g) was treated with trifluoroacetic acid (3ml) and stirred at 22°C for 2h. The solvent

was evaporated *in vacuo*, and the residue was purified by preparative HPLC (gradient profile 20-70% (ii) in 18 min, R_f 12.5min). Trituration with ether to give the title compound as a white crystalline solid (0.114g).

Mass spectrum m/z 447.2 (MH⁺)

5 Analysis Found: C, 44.5; H, 4.7; N, 7.7.

C₂₂H₃₀N₄O₄S.2.4C₂HF₃O₂ requires C, 44.7; H, 4.5; N, 7.8%.

Example 6

10 Synthesis of {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid.

Method A

A solution of {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid trifluoroacetate (690 mg) in water (90 ml) was added to a stirred suspension of 10% palladium on carbon (600 mg) in water (30 ml) and the mixture stirred at 23° under nitrogen for 6h. The catalyst was
15 filtered off and the filtrate evaporated *in vacuo* to give title compound as fine white crystals (420 mg).

Mass spectrum m/z 449 (MH⁺)

Analysis. Found: C, 42.6; H, 4.9; N, 7.2.

20 C₂₂H₃₂N₄O₄S.3C₂HF₃O₂.0.3C₄H₁₀O requires C, 42.4; H, 4.6; N, 6.8%.

Method B

(a) 4-{2-[1-Methanesulfonyl-3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

25 Methanesulphonyl chloride (7.6 ml) was added dropwise to a stirred solution of 4-{2-[3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (40.1 g), and 4-N,N-dimethylaminopyridine (0.96 g) in pyridine (280 ml) at ambient temperature. The resulting brown solution was stirred at ambient temperature for 18h, diluted with water (400 ml) and extracted with dichloromethane (400 ml). The combined
30 organic extracts were evaporated *in vacuo*, the brown residue diluted with ethanol (400 ml) and evaporated *in vacuo* to give a brown oil. The oil was triturated with ethanol (400 ml) and evaporated *in-vacuo* to ca 200 ml to give a suspension. The resulting solid was isolated by filtration, washed with ethanol

and dried in vacuo at 45°C to give the title compound as an off-white solid (37.6 g).

Mass spectrum m/z 605 (MH⁺)

5 **(b) {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid**

A solution of 4-{2-[1-methanesulfonyl-3-(1-tert-butoxycarbonylmethyl-piperidin-4-yl)-1H-indazol-6-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (20 g) in 5N hydrochloric acid (200 ml) was stirred at ambient temperature for 5h. The reaction mixture was neutralised with saturated potassium carbonate (300 ml) and extracted with isopropanol. The combined organic extracts were evaporated in vacuo to give an oil which was diluted with ethanol (300 ml) and concentrated by rotary evaporation to give a white solid. The off-white solid was purified by flash chromatography (Merck 9385) eluting with ethanol : dichloromethane: 0.88 ammonia (gradient: 15:3:1 to 15:3:1.5) afforded the title compound as a white solid (10.1 g).

Analysis found: C,56.3; H,7.7; N,11.0 %

(C₂₂H₃₂N₄O₄S. 0.80 H₂O. 0.83 C₂H₆O) x 0.984 requires: C, 55.8; H, 7.6; N, 11.1 %

20 **Example 7 - Tablets**

25	a)	Compound of the invention	5.0mg
		Lactose	95.0mg
		Microcrystalline Cellulose	90.0mg
		Cross-linked polyvinylpyrrolidone	8.0mg
		Magnesium Stearate	2.0mg
		Compression weight	200.0mg

30 The compound of the invention, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

35	b)	Compound of the invention	5.0mg
		Lactose	165.0mg

Pregelatinised Starch	20.0mg
Cross-linked polyvinylpyrrolidone	8.0mg
Magnesium Stearate	<u>2.0mg</u>
Compression weight	200.0mg

- 5 The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

10

Example 8 - Capsules

a)	Compound of the invention	5.0mg
	Pregelatinised Starch	193.0mg
	Magnesium Stearate	<u>2.0mg</u>
15	Fill weight	200.0mg

- 20 The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.

b)	Compound of the invention	5.0mg
	Lactose	177.0mg
	Polyvinylpyrrolidone	8.0mg
	Cross-linked polyvinylpyrrolidone	8.0mg
25	Magnesium Stearate	<u>2.0mg</u>
	Fill weight	200.0mg

- 30 The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules of a suitable size.

Example 9 - Syrup

a)	Compound of the invention	5.0mg
35	Hydroxypropyl Methylcellulose	45.0mg

	Propyl Hydroxybenzoate	1.5mg
	Butyl Hydroxybenzoate	0.75mg
	Saccharin Sodium	5.0mg
	Sorbitol Solution	1.0ml
5	Suitable Buffers	qs
	Suitable flavours	qs
	Purified Water to	10.ml

The hydroxypropyl methylcellulose is dispersed in a portion of hot purified water together with the hydroxybenzoates and the solution is allowed to cool to ambient temperature. The saccharin sodium flavours and sorbitol solution are added to the bulk solution. The compound of the invention is dissolved in a portion of the remaining water and added to the bulk solution. Suitable buffers may be added to control the pH in the region of maximum stability. The solution is made up to volume, filtered and filled into suitable containers.

Example 10 - Injection Formulation

		% w/v
	Compound of the invention	1.00
	Water for injections B.P. to	100.00
20	Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included. The solution is clarified, made up to final volume with water and the	
25	pH remeasured and adjusted if necessary, to provide 10mg/ml of the compound of formula (I).	

The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes may be aseptically filled (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

Preferably the solution is filled into ampoules, sealed by fusion of the glass and terminally sterilised.

Further sterile formulations are prepared in a similar manner containing 0.5, 2.0 and 5% w/v of the compound of formula (I), so as to provide respectively 5, 20 and 50mg/ml of the compound of formula (I).

5 Biological Data

1. Human Washed Platelets Assay

Inhibition of platelet aggregation by compounds of the invention was determined according to the following procedure. Citrated whole blood (1 part 3.8% w/v trisodium citrate; 9 parts blood) was obtained from human volunteers, free of medication for at least 10 days prior to donation. The blood was treated with aspirin (0.1mM) and prostacyclin (0.06 μ M) prior to centrifugation (1400g, 4 minutes, 20°C). The supernatant platelet-rich plasma (PRP) was isolated and further centrifuged (1400g, 10 minutes, 20°C) to sediment the platelets. The supernatant was discarded and the platelet pellet resuspended into a physiological salt solution (HEPES 5mM, NaHCO₃ 12mM, NaCl 140mM, KH₂PO₄ 0.74mM, D-Glucose 5.6mM and KCl 2.82mM) adjusted to pH 6.4. This platelet suspension was centrifuged (1400g, 8 minutes, 20°C) and the resultant platelet pellet was resuspended into the physiological salt solution adjusted to pH 7.4. The resultant washed-platelet preparation was diluted to give a final platelet count of 3x10⁸/l. Purified human fibrinogen (Knight, L.C. *et al.*, 1981 Thromb. Haemostasis, 46, (3), 593-596), Ca²⁺ and Mg²⁺ were added back to the washed platelet preparation to give final concentrations of 0.5mg/ml, 1mM and 0.5mM respectively. Platelet aggregation was quantified using a turbidometric method. Test compounds were incubated with the washed platelets (37°C) for 5 minutes prior to the addition of 1 μ M of the platelet aggregatory agonist U-46619 (a stable thromboxane A₂-mimetic). The inhibitory potency of the test compounds was expressed as an IC₅₀ value, which is defined as the concentration of the compound required to inhibit platelet aggregation by 50%. The following IC₅₀ values were obtained for compounds of the invention:

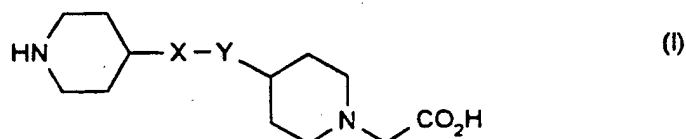
Table 1

Example no.	IC ₅₀ (nm)
1	100
2	53
3	<100

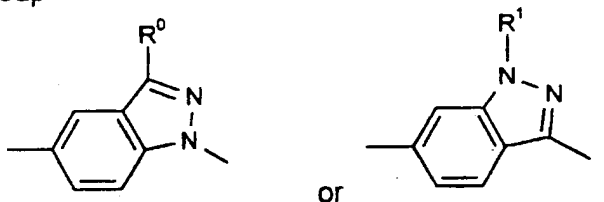
4	<100
5	<100
6	<100

CLAIMS

1. A compound of formula (I)

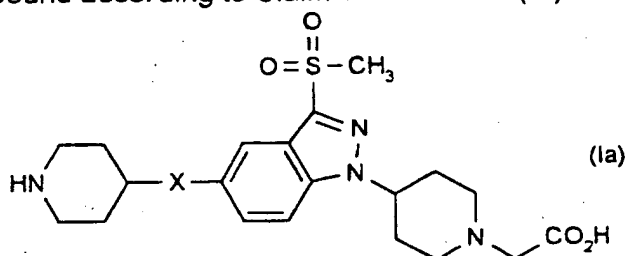


- 5 or a salt, solvate, or physiologically functional derivative thereof, in which:
X represents either $\text{CH}_2\text{-CH}_2$ or CH=CH ;
Y represents a group



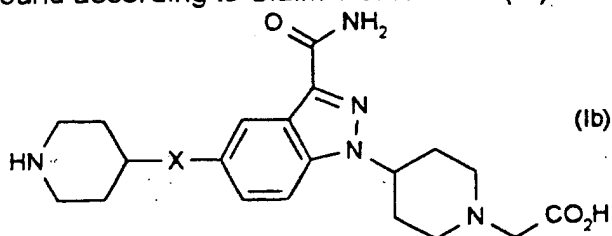
- 10 R^0 represents SO_2Me or CONH_2 ; and
 R^1 represents SO_2Me .

2. A compound according to Claim 1 of formula (Ia)



- 15 or a salt, solvate, or physiologically functional derivative thereof, in which
X represents either $\text{CH}_2\text{-CH}_2$ or CH=CH .

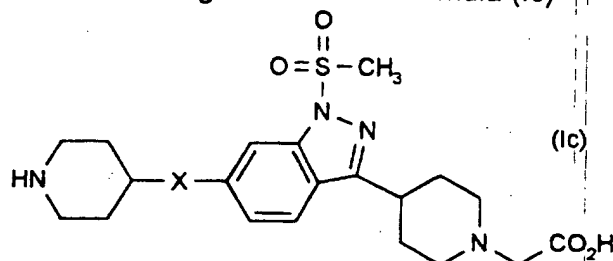
3. A compound according to Claim 1 of formula (Ib)



- or a salt, solvate, or physiologically functional derivative thereof, in which

X represents either CH₂-CH₂ or CH=CH.

4. A compound according to Claim 1 of formula (Ic)



- 5 or a salt, solvate, or physiologically functional derivative thereof, in which X represents either CH₂-CH₂ or CH=CH.

5. {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl} acetic acid;
- 10 {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid ;
- {4-[3-carbamoyl-5-(2-piperidin-4-yl-(E)-vinyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
- {4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
- 15 {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-(E)-vinyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
- {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
- 20 and salts, solvates, and physiologically functional derivatives thereof.

6. {4-[3-methanesulfonyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
- {4-[3-carbamoyl-5-(2-piperidin-4-yl-ethyl)-indazol-1-yl]-piperidin-1-yl}-acetic acid;
- 25 {4-[1-methanesulfonyl-6-(2-piperidin-4-yl-ethyl)-1H-indazol-3-yl]-piperidin-1-yl}-acetic acid;
- or a salt, solvate, or physiologically functional derivative thereof.

7. A compound according to any of Claims 1-6 which is a hydrochloride salt.

5 8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof in admixture with one or more physiologically acceptable carriers or excipients.

10 9. A compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

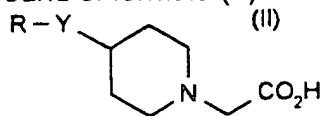
15 10. Use of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof in the manufacture of a therapeutic agent for the treatment of thrombotic disorders.

20 11. A method of treating a human or animal subject suffering from a condition which is mediated through the Glycoprotein complex GpIIb/IIIa or other integrin receptor which comprises administering to said subject an effective amount of a compound according to any one of claims 1 to 7 or a pharmaceutically acceptable derivative thereof.

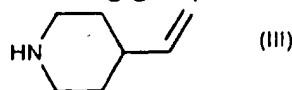
12. A method according to claim 11 wherein the condition is a thrombotic disorder.

25 13. A process for the preparation of a compound as defined in any one of claims 1 to 7, which comprises:

(A) reaction of a compound of formula (II)



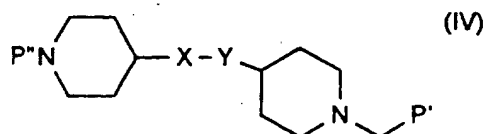
30 or a protected derivative thereof, wherein Y is as defined for a compound of formula (I) and R represents a leaving group, with a compound of formula (III)



or a protected derivative thereof; or

(B) interconversion using a compound of formula (I) or a protected derivative thereof as a precursor; and/or

(C) deprotection of a compound of formula (IV),



5

wherein X and Y are as defined for a compound of formula (I), P' is a carboxyl group or a protected carboxyl group and P'' is hydrogen or an amino protecting group, provided that when P' is a carboxyl group, P'' is not hydrogen, P' is a hydrogen, P'' is not a carboxyl group and/or optionally converting the resultant

10

compound of formula (I) into a pharmaceutically acceptable derivative thereof.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 97/03196

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/14 A61K31/415 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 22303 A (GLAXO GROUP LTD ;MIDDLEMISS DAVID (GB); JUDKINS BRIAN DAVID (GB);) 11 November 1993 see the whole document ----	1-13
A	EP 0 542 363 A (GLAXO GROUP LTD) 19 May 1993 see the whole document ----	1-13
A	EP 0 525 629 A (THOMAE GMBH DR K) 3 February 1993 see the whole document -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

26 September 1997

Date of mailing of the international search report

08.10.97

Name and mailing address of the ISA

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Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 97/03196

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 11 and 12
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/EP 97/03196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 5221999 A	31-08-93
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		ZA 9205573 A	24-01-94

